

Sub 1
B1

(i) transforming a [eucaryotic] eukaryotic cell with a first DNA [sequence] construct encoding a first indicator component under the control of a promoter having restricted expression;

(ii) transforming the cell of (i) or a descendent of the cell by operably integrating into the cell's genome, a second DNA construct comprising DNA [lacking a promoter but which comprises a sequence] encoding a second indicator component not operably linked to a transcription control element;

(iii) producing tissue or specialized cells from the cell of (ii); and

(iv) monitoring the tissue or specialized cells of (iii) for a detectable indicator resulting from both the first and second indicator components indicative of integration of the second DNA construct into a gene having restricted expression.

Sub 2
B2

6. (Amended) The method of [any one of claims 1-5] claim 1 which additionally comprises [the additional step of] isolating DNA endogenous to the eucaryotic cell which flanks [integrated DNA comprising the second indicator component] the second DNA construct integrated into a gene having restricted expression.

Sub C1
B3

9. (Amended) A DNA construct comprising, in a 5' to 3' direction, a splice acceptor, [and] a sequence encoding an inactive subunit or fragment of an enzyme and, an IRES wherein said sequence encoding is not operably linked to a transcription control element, and wherein said subunit or fragment is active when combined with a further subunit or fragment of an enzyme.

Sub C2
B4

12. (Amended) The combination of:

(i) a DNA construct for integration into the genome of an [eucaryotic] eukaryotic cell comprising a sequence encoding a first indicator component under the control of a promoter having restricted expression; and

(ii) a DNA construct for integration into the genome of a [eucaryotic] eukaryotic cell, comprising in the 5' to 3' direction, a splice acceptor, [and] a sequence encoding a second indicator component not operably linked to a transcription control

B⁴
8 ~~element and an optional IRES, wherein expression of both the first and second indicator~~
9 ~~components in said cell is detectable.~~

Please add the following new claims:

1 ~~sub C³~~ --15. A DNA construct comprising, in a 5' to 3' direction, a ~~splice acceptor~~
2 and a sequence encoding an inactive ~~alpha or omega~~ fragment of β -galactosidase, wherein said
3 sequence encoding is not operably linked to a transcription control element and said fragment
4 is active when combined with another fragment of β -galactosidase.

B⁵
1 ~~sub D²~~ 16. The method of claim 1, wherein:
2 (i) in the first DNA construct, DNA encoding the first indicator
3 component is separated from the promoter having restricted expression by a sequence of DNA
4 which prevents transcriptional control by said promoter over the DNA encoding the first
5 indicator component;
6 (ii) in the second DNA construct, the second indicator component is
7 a recombinase capable of removing the sequence of DNA preventing transcriptional control in
8 the first DNA construct; and,
9 wherein said monitoring is for cells in which the first indicator
10 component is expressed under the transcriptional control of the promoter having restricted
11 expression.

1 11 ~~17~~ 17. The method of claim ~~16~~¹⁵ wherein the DNA preventing transcriptional
2 control is flanked by lox sites and the recombinase is Cre.

sub D⁴
1 18. A method of producing eukaryotic tissue or specialized cells comprising
2 a detectable indicator associated with a target gene having restricted expression, which
3 comprises:
4 (i) transforming a eukaryotic cell with a first DNA construct
5 encoding a first indicator component under the control of a promoter having restricted
6 expression;

Sub 4
7 (ii) transforming the cell of (i) or a descendent of the cell by
8 integrating into the cell's genome, a second DNA construct comprising DNA encoding a
9 second indicator component not operably linked to a transcription control element;
10 (iii) producing tissue or specialized cells from the cell of (ii); and
11 (iv) selecting tissue or specialized cells of (iii) by the presence of a
12 detectable indicator resulting from both the first and second indicator components.

B5
Sub c4 19. A method of producing a mouse or a pig comprising a detectable
2 indicator associated with a target gene having restricted expression, which comprises:
3 (i) transforming a murine or porcine ES cell with a first DNA
4 construct encoding a first indicator component under the control of a promoter having
5 restricted expression;
6 (ii) transforming the cell of (i) or a descendent of the cell by
7 integrating into the cell's genome, a second DNA construct comprising DNA encoding a
8 second indicator component not operably linked to a transcription control element;
9 (iii) selecting transformed cells of (ii);
10 (iv) introducing selected cells of (iii) into a murine or porcine host
11 embryo;
12 (v) implanting the host embryo of (iv) into a pseudopregnant
13 mammal;
14 (vi) maintaining the mammal of (v) while offspring develops to term
15 from the host embryo; and
16 (vii) selecting offspring of (vi) by the presence of a detectable
17 indicator resulting from both the first and second indicator components in tissue or specialized
18 cells of the offspring.--

REMARKS

In the Office Action, claims 7-14 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Claims 1-8 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claim 9 was rejected under 35 U.S.C. § 102(b) as allegedly